A new efficient synthesis of pyridines

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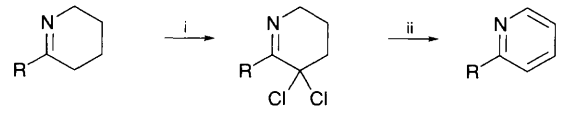
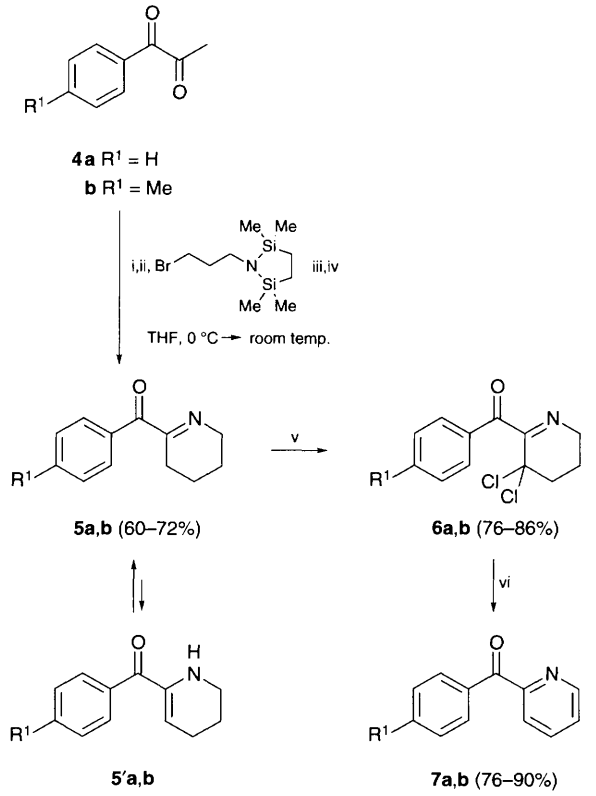
Cyclic six-membered imines, *i.e.* 2,3,4,5-tetrahydropyridines, are efficiently converted under mild conditions into the corresponding pyridines by highly regioselective α, α-dichlorination with *N*-chlorosuccinimide (NCS) followed by double dehydrochlorination with methanolic bases.

Pyridines hold a major position in heterocyclic chemistry because of their numerous applications in agro- and pharmaceutical chemistry.[1] The identification of pyridines as characteristic flavour compounds in peppermint,[2,3] spearmint,[2,4] tobacco[5] and orange oil has also raised considerable interest.[6] Other simple pyridines were found as alkaloids in alfalfa,[7] red clover[7] and various other plant sources.[1] Owing to the potential physiological activities and synthetic value of pyridines, a lot of syntheses of pyridines have been reported so far.[8,9] Because of the ready accessibility of cyclic six-membered imines, *i.e.* 2,3,4,5-tetrahydropyridines, a straightforward synthesis of pyridines would consist of the dehydrogenation of the former heterocycles. This attractive route has only been used in a very few cases as a synthetic strategy for pyridines. The major drawback of this dehydrogenation process is the harsh conditions of the reaction, *e.g.* heating under reflux in xylene in the presence of nitrobenzene and palladium on carbon.[10,11] The related 1,2,3,6-tetrahydropyridines have been dehydrogenated into pyridines under similar drastic conditions, *e.g.* heating under reflux for 36 h in mesitylene in the presence of selenium[12] or in nitrobenzene in the presence of palladium on alumina.[13] The dehydrogenation of highly functionalized 5-cyano-1,2,3,4-tetrahydropyridine with 5,6-dichloro-2,3-dicyano-1,4-benzoquinone afforded extremely low yields of the required pyridine product.[14] Only a very limited number of annellated polycyclic pyridine derivatives, *e.g.* 6-azaquinazolines or β-carbolines, utilizing palladium on carbon in nitrobenzene[15] or manganese dioxide,[16] have been synthesized. Here we report a facile and mild two step synthesis of pyridines from tetrahydropyridines.

2,3,4,5-Tetrahydropyridines **1** are accessible from the cyclization of imines (or imino derivatives) with 3-halopropylazides[17,18] or ethylenetetramethyldisilyl-protected 3-bromopropylamine.[19] Alternatively, heterocycles **1** are synthesized by boric acid induced alkoxydecarbonylation of enaminoesters.[20] α,α-Dichlorination of 6-aryl-2,3,4,5-tetrahydropyridines **1a–d** with 2.5 equiv. of *N*-chlorosuccinimide in tetrachloromethane at room temperature for 15 h or under reflux for 5–10 min afforded the new 5,5-dichloro-2,3,4,5-tetrahydropyridines **2a–d** in 93–94% yield. Aliphatic tetrahydropyridines **1e–h** showed a high degree of regioselectivity upon reaction with 2 equiv. of *N*-chlorosuccinimide in CCl_4, leading to 6-alkyl-5,5-dichloro-2,3,4,5-tetrahydropyridines **2e–h** in 81–87% yield. This regioselective reaction can be performed at room temperature (3 h) or at reflux for 1–5 min. Attempts to obtain the corresponding monochloroimines by reaction with 1 equiv. of *N*-chlorosuccinimide failed due to the obtension of a mixture of α-monochloro- and α,α-dichloro-imines, and the starting material in equal amounts (*ca.* 1 : 1 : 1). Treatment of α,α-dichloroimines **2a–h** with 5 equiv. of 2 mol dm^{-3} sodium methoxide in methanol at room temperature (15 h) or under reflux (5–15 h) provided the pyridines **3a–h** in 91–95% yield. It has to be reported that, in the case of the pyridyl-substituted tetrahydropyridines **1c,d** both the α,α-dichlorination and subsequent dehydrochlorination steps can only be performed at room temperature. The application of reflux conditions for these



Scheme 1 *Reagents and conditions*: i, NCS (2.5 equiv. for **a–d**; 2.0 equiv. for **e–h**), room temp., 3–15 h or heat, 1–10 min; ii, NaOMe (5 equiv., 2 mol dm^{-3}), MeOH, heat, 5–15 h or room temp., 15 h

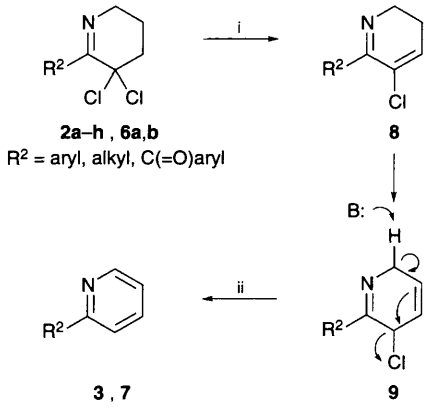


Scheme 2 *Reagents and conditions*: i, Pr^iNH_2, $TiCl_4$, C_6H_6; ii, LDA, THF, 0 °C; iii, K_2CO_3, MeOH; iv, oxalic acid, H_2O; v, NCS (2.5 equiv.), CCl_4, room temp., 15 h; vi, K_2CO_3, THF, heat, 3 h; or NaOMe (2 mol dm^{-3}), MeOH, heat, 3 h

derivatives led to a complex reaction mixture of degenerated aromatic compounds.

This two step procedure from tetrahydropyridines **1** gave access to pyridines **3** in excellent overall yields and with virtually no impurities present, making additional purification steps almost unnecessary (Scheme 1). This synthetic procedure is exemplified for the synthesis of 2-phenylpyridine **3a**, which is a natural flavour compound of orange oil.[6] In addition, the ready access to the alkaloid isonicoteine **3c**, a neurotoxin isolated from the carnivorous marine worm Hoplonemertine sp.,[21] the bidentate oligopyridine 2,2′-bipyridine **3d**[22] and the bontebok pheromone 2-heptylpyridine **3h**[23] underline the simplicity and the synthetic potential of this procedure. Functionalized pyridines can be synthesized as well, as illustrated for the synthesis of 2-aroylpyridines **7** (Scheme 2). 6-Aroyl-2,3,4,5-tetrahydropyridines **5** were prepared from 1-aryl-1,2-propanediones **4** by a sequence of reactions involving (i) double imination with isopropylamine in the presence of stoichiometric amounts of titanium(IV) chloride,[24] (ii) α-alkylation with stabase-protected 3-bromopropylamine,[25] (iii) deprotection and ring closure. Similar as described above, α,α-dichlorination of **5**, which occurs in equilibrium with the enamine form **5′** [^{1}H NMR ($CDCl_3$): **5**/**5′** = 76–80/24–20], and subsequent dehydrochlorination with potassium carbonate (3 equiv.) in THF (reflux, 3 h) or sodium methoxide (3 equiv.; 2 mol dm^{-3}) in methanol (reflux, 3 h) resulted in the formation of 2-benzoylpyridine **7a** and 2-(4′-methylbenzoyl)pyridine **7b** in 90% (K_2CO_3) and 76% (K_2CO_3) yield, respectively. The use of sodium methoxide in methanol generally led to lower yields.

From the mechanistic point of view, α,α-dichloroimines **2** and **6** are most probably 1,2-dehydrochlorinated by the base to give an intermediate 1-aza-1,3-diene **8**, which suffers base-induced deconjugation into **9**, the latter being 1,4-dehydrochlorinated to afford pyridines **3** and **7** (Scheme 3).



Scheme 3 *Reagents*: i, NaOMe or K_2CO_3, MeOH; ii, −HCl

The present methodology is attractive because of its ease of operation, mild reaction conditions, absence of side products and high yields. It is a useful addition to the arsenal of known pyridine syntheses.

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